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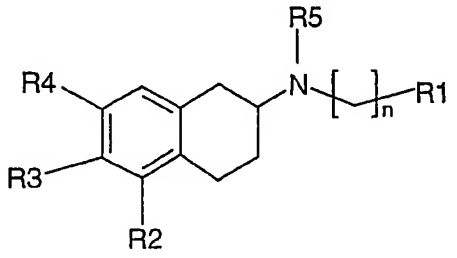
(54) UTILISATION DE 2-AMINOTETRALINES SUBSTITUEES POUR LE TRAITEMENT PROPHYLACTIQUE DE LA MALADIE DE PARKINSON

(54) USE OF SUBSTITUTED 2-AMINOTETRALINES FOR THE PREVENTATIVE TREATMENT OF PARKINSON'S DISEASE

(57)

The invention relates to the use of substituted 2-aminotetralines of general formula (I) as a medicament for the preventative treatment of Parkinson's disease.



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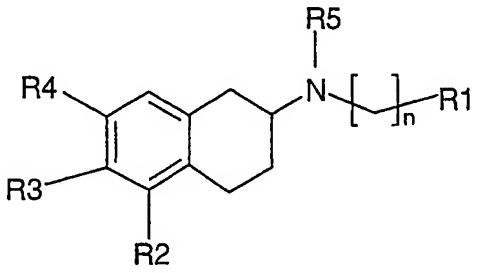

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(57) Abrégé/Abstract:
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ABSTRACT

The invention relates to the use of substituted 2-aminotetralines of general formula (I) as a medicament for the preventative treatment of Parkinson's disease.

Use of Substituted 2-Aminotetralines for the Preventative Treatment of Parkinson's Disease

Parkinson's disease occurs as a result of a chronic, progressive degeneration of neurones, the cause of which has not yet been completely clarified. It is clinically manifested in the form of the cardinal symptoms of resting tremors, rigidity, bradykinesia and postural instability.

Primarily used as medicaments for alleviating the motor symptoms are levodopa, dopamine agonists such as, for example, rotigotine, pramipexole, bromocriptine, ropinirole, cabergoline, pergolide, apomorphine and lisuride, anticholinergic agents, NMDA antagonists, β-blockers as well as the MAO-B inhibitor selegeline and the COMT inhibitor entacapone. Most of these active substances intervene in the dopaminergic and/or cholinergic signal cascade and symptomatically influence in this manner the motor disturbances that are typical of Parkinson's disease.

The therapy of Morbus Parkinson has, to date, been initiated with the onset of the cardinal symptoms. Morbus Parkinson is generally deemed to be clinically confirmed if at least two of the four cardinal symptoms (bradykinesia, resting tremors, rigidity and postural instability) can be determined and L-Dopa has an effect (Hughes, J Neurol Neurosurg Psychiatry 55, 1992, 181). Unfortunately, however, patients with Parkinson's disease only develop the motor disturbances once approximately 70 to 80% of the dopaminergic neurones in the substantia nigra (SN) have been irreversibly damaged (Becker *et al*, J Neurol 249, 2002, Suppl 3: III, 40; Hornykiewicz, Encyclopaedia of Life Science 2001, 1). The chances of a therapy with lasting effects are minimal at this time. It is thus desirable to commence therapy as early as possible.

Current clinical observations as well as anatomical and genetic research now show that it is possible to both diagnose patients with Parkinson's disease at an early stage and to identify high-risk patients.

The following, for example, can thereby be used as diagnostic markers:

- Biochemical markers, such as neuromelanin (Gerlach, Neurotox Res 5, 2003, 35; WO 02/31499), S-100 beta (Muramatsu, Glia 42, 2003, 307), alpha synuclein (WO 03/069332; WO 00/02053) or parkin protein (Sharma, Neurol Clin N Am 20, 2002, 759) and semaphorin (WO 03/007803).

- Genetic markers, such as the park genes 1-8 (Guttman, CMAJ 4, 2003, 168); CYP2D6-B (WO 03/012137), chromosome 2q 36-37 (Pankratz, Am J Hum Gen 72, 2003, e-pub), a-synuclein (Polymeropoulos, Science. 276, 1997, 2045) or mutations in CYP2D6-B and GSTM1 deletion (WO 03/012137).
- Imaging methods, such as ultrasound examination of the SN size, possibly in combination with other methods (Becker *et al*, J Neurol 249, 2002, Suppl 3: III, 40) or MRI (Hutchinson M, Raff U., J Neurol Neurosurg Psychiatry. 1999 Dec; 67(6): 815-8).
- Imaging methods such as PET or SPECT (Prunier C, Bezard E *et al*, Neuroimage. 2003 July; 19(3): 810-6).
- Sensory disorders or behavioural abnormalities, such as sleep and olfactory disorders, in particular, sleep disorders of the type "REM behaviour disorder", (Henderson, J Neurol Neurosurg Psychiatry 74, 2003, 956) or cognitive abnormalities (Rammsayer, Int J Neurosci. 91, 1997, 45).
- Organic problems such as constipation (Krygowska-Wajs, Funct Neurol 15, 2000, 41).
- Depression (Camicioli R. Drugs Today (Barc). 2002 Oct; 38(10): 677-86).
- Short-term movement anomalies, such as chorea or orthostatic abnormalities.
- Combinations of the aforementioned markers (Stern, Annals of Neurol 56, 2004, 169).

This thus creates the opportunity to influence the process of the disease at a point when more neurones are still present than is the case at the time of onset of several cardinal motor symptoms of Morbus Parkinson, and to thus protect a quantitatively greater number of neurones. It can be expected that the administration of an effective neuroprotective agent at an early stage will significantly delay the disease process: The earlier a therapy can be initiated, the greater the chances of a long-lasting prevention of the onset of symptoms that lower the quality of life.

There is thus a need for medicaments that are not only able to influence dopaminergic transmission and alleviate the symptoms of Morbus Parkinson in advanced stages, but that are also able to reverse, prevent or at least significantly slow down the progressive destruction of dopaminergic neurones in the early, largely motor-asymptomatic stages of Parkinson's disease (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

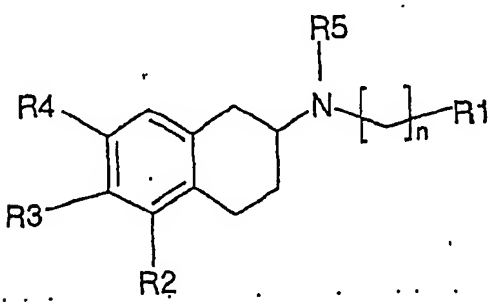
Substituted 2-aminotetralines are known from US 4,564,628, US 4,885,308, US 4,722,933 and WO 01/38321. These are substances having a dopaminergic effect, which are known for the symptomatic treatment of Parkinson's disease. In clinical studies, rotigotine [(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] in particular has proven itself to be an effective transdermally available anti-Parkinson drug. WO 02/

089777 describes, for example, the transdermal administration of rotigotine to patients with Parkinson's disease and the associated improvement in the UPDRS (Unified Parkinson's Disease Rating Scale) score. The UPDRS score is an important instrument for diagnosing and monitoring the progression and/or therapy of patients with Parkinson's disease (Fahn S, Elton RL, Members of the UPDRS Development Committee (1987) Unified Parkinson's Disease Rating Scale. In: Fahn, S, CD Marsden, DB Calne, M Goldstein (eds) Recent Developments in Parkinson's Disease. Vol. II. Macmillan Healthcare Information, Florham Park (NJ), pages 153-163, 293-304). However, the UPDRS score only records the effect of an active substance on the symptoms of Parkinson's disease. It does not allow any statements to be made with regard to whether or not an active substance has an influence on the destruction of dopaminergic cells, which is the underlying cause of the symptoms.

Metman *et al* (Clin Neuropharmacol 24, 2001, 163) also describe the effect of rotigotine on motor disturbances associated with Parkinson's disease. The treated patients already had pronounced dyskinesias, which were improved by administering rotigotine.

Thus, substituted 2-aminotetralines, in particular rotigotine, are known from the prior art as a dopamine agonist for the symptomatic treatment of Parkinson's disease. However, Parkinson medicaments that only have an effect on the symptoms do not promise any advantage with regard to the preventive treatment of Parkinson's disease since they do not have any influence on the destruction of dopaminergic cells or on the progression and/or onset of the disease.

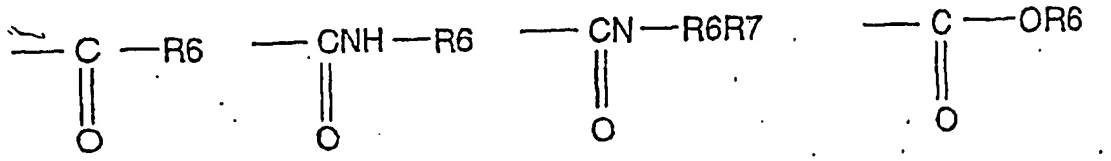
Experimental tests have now surprisingly shown that the substituted 2-aminotetralines of the general formula I



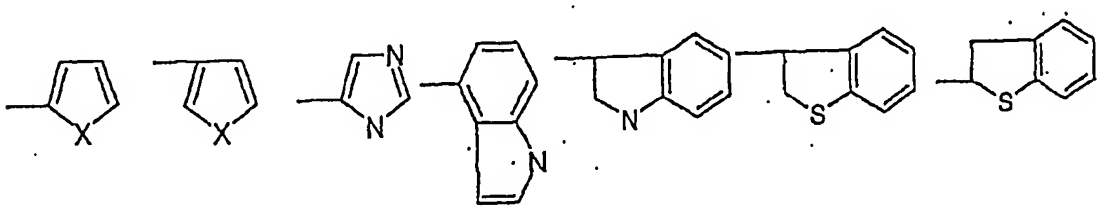
wherein

n is 1 to 5;

R2 is OA; R3 and R4 are each independently selected from H and OA; with A being selected from H, alkyl, alkoxymethyl or a group



wherein R6 and R7 are each independently alkyl, in particular C1-20 alkyl and particularly preferred C1-6 alkyl, or aryl, in particular optionally substituted phenyl;
R5 is a C1-3 alkyl;
R1 is a group selected from hydrogen, 3-pyridyl, 4-pyridyl, optionally substituted phenyl,



wherein X is selected from S, O or NH;

wherein the compound of formula I can be present as a racemate or as a pure (R)- or (S)-enantiomer,

as well as physiologically acceptable salts of these compounds,

which had hitherto only been used for the symptomatic therapy of Parkinson's disease, have neuroprotective properties and they can thus be used as a medicament and/or prophylactic agent for the prevention of dopaminergic cell loss in particular in very early stages of Parkinson's disease or in high-risk patients.

Figures

Fig. 1 shows representative examples of the neuroprotective effect of rotigotine measured on the basis of the density of the dopamine transporters as an indication of the density of the remaining nerve endings in the striatum.

Groups 1 to 7 were treated as follows: Group 1: untreated control group; Group 2: control group treated with a vehicle solution for rotigotine and MPTP; Group 3: MPTP treatment; Group 4: MPTP treatment plus rotigotine 0.3 mg/kg; Group 5: MPTP treatment plus

rotigotine 1.0 mg/kg; Group 6: MPTP treatment plus rotigotine 3.0 mg/kg; Group 7: treatment solely with rotigotine (3.0 mg/kg).

Fig. 2 shows dopamine transporter (DAT) binding in the dorsal and ventral part of the striatum in different groups by quantifying the DAT density according to an experiment as shown in Fig. 1. Bar graphs 1 to 7 correspond to groups 1 to 7 as shown in Fig. 1. The groups marked with * displayed a significant decline in DAT binding as compared to the control group 2. The groups marked with # displayed a significant gain in DAT binding as compared to the MPTP-treated Group 3.

Description of the Invention

Apoptotic processes are supposed to play an important role in the destruction of dopaminergic neurones in the pathogenesis of Parkinson's disease (Barzilai, Cell Mol Neurobiol 21, 2001, 215). Neuroprotective substances that can stop or even reverse dopaminergic cell destruction are thus desired. The MPTP model is thereby deemed to be predictive of the required neuroprotective characteristics (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

Rotigotine surprisingly shows the desired pharmacological profile in both an acute and a sub-acute MPTP model. The test results suggest that apoptotic processes are prevented by rotigotine.

The 2-aminotetralines according to the invention, in particular rotigotine, thereby display a neuroprotective effect in a mouse model of Parkinson's disease: Following the acute administration of MPTP, which causes Parkinson's syndrome in both humans and monkeys, the number of the degenerating neurones in the acute phase was measured on the one hand (Table 1) and the functional integrity of the striatum in the sub-acute phase was ascertained on the other by determining the density of the dopamine transporter in the terminal nerve endings (Figs. 1 and 2). It could be demonstrated in both cases that rotigotine had a neuroprotective effect: On the one hand, the number of degenerating neurones in the mesencephalon was reduced following the administration of rotigotine and on the other hand, the dopaminergic innervation of the striatum was almost completely maintained or restored.

Table 1: Number of degenerating neurones in the mouse, shown by FluoroJade staining

Group	No. of degenerating neurones	Standard deviation
1: Vehicle-treated control group	2.0	2.4
2: MPTP intoxication	73.5	34.0
3: MPTP intoxication + rotigotine 0.3 mg/kg	66.7	30.5
4: MPTP intoxication + rotigotine 1.0 mg/kg	76.8	41.6
5: MPTP intoxication + rotigotine 3.0 mg/kg	34.9	31.9
5: MPTP –vehicle + rotigotine 3.0 mg/kg	3.8	4.3

In a pilot study, the neuroprotective effect of rotigotine on monkeys was also examined.

In the model used, which reflects the progressive course of Morbus Parkinson in primates, monkeys (macaques) were injected with subliminal toxic doses of MPTP for several days. Parkinson's symptoms developed in the model over a period of approximately 2 weeks. As soon as a certain level of damage had been reached, rotigotine was injected daily in a formulation that produced a continuous plasma level over 24 hours. The MPTP injections were stopped as soon as the motor activity had been reduced to a certain extent (approximately 5 days later). The behaviour of the animals was assessed on a daily basis. Six weeks after the start of MPTP administration, the rotigotine injections were stopped and the animals were observed for a further two weeks without treatment. It was observed that the motor activity of the animals clearly improved during treatment and also in the following clearance phase.

A group of animals was killed at the end of both the rotigotine administration and the clearance phase, and the condition of the basal ganglia was histologically and biochemically examined. The density of the nerve endings in the striatum had significantly increased as compared to the untreated animals. The content of pre-pro-enkephalin, which is an indicator of the intact network in the "indirect pathway" of the basal ganglia, showed a tendency towards normalisation following treatment and the clearance phase.

The results show that the neuroprotective potential of rotigotine can also be proven in a primate model of Morbus Parkinson. A neuroprotective effect can therefore also be expected in humans.

Thus, with rotigotine and structurally related substituted 2-aminotetralines of the general formula I, active substances were provided for therapy, which are ideally suitable for

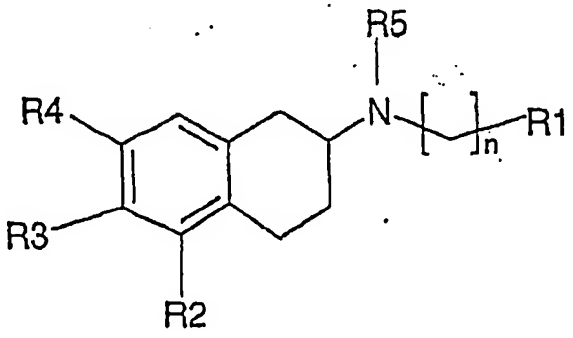
producing medicaments and/or prophylactic agents for the prevention of dopaminergic neurone loss.

A subject matter of the present application is therefore the use of substituted 2-aminotetralines of the general formula I, which is given below, as well as, in particular, rotigotine for the production of a medicament for the treatment or prevention of dopaminergic neurone loss in patients suffering from a neurodegenerative disease that is associated with increased dopaminergic cell destruction or in patients having an increased risk of augmented dopaminergic cell destruction.

Increased dopaminergic neurone loss regularly occurs in patients with Parkinson's disease, however, it is also frequently observed in other neurodegenerative diseases, for example, in alpha-synucleopathies or in Huntington's disease as well as in REM sleep disturbances and olfactory disorders.

As compared to the hitherto use of the aminotetralines of formula I, in particular rotigotine, which was limited solely to the symptomatic treatment of Parkinson's patients with motor disturbances, the prophylactic treatment of individuals displaying less than two of the cardinal symptoms of Parkinson's disease and who thus require neuroprotective, prophylactic therapy rather than symptomatic therapy, has been developed as a new area of use. As already described above, such individuals profit in particular from the neuroprotective effect of rotigotine since owing to the administration of rotigotine, dopaminergic cell loss is stopped or slowed down at a time when a higher number of dopaminergic neurones are still present than is the case in patients already displaying motor symptoms.

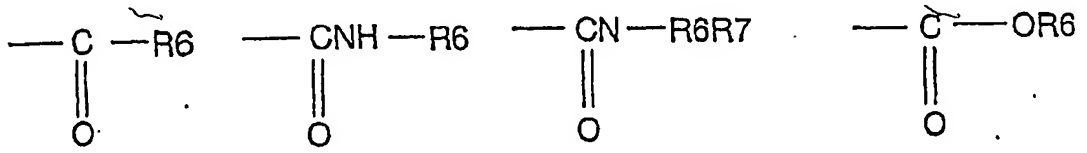
A subject matter of the invention is therefore the use of substituted 2-aminotetralines of the general formula I



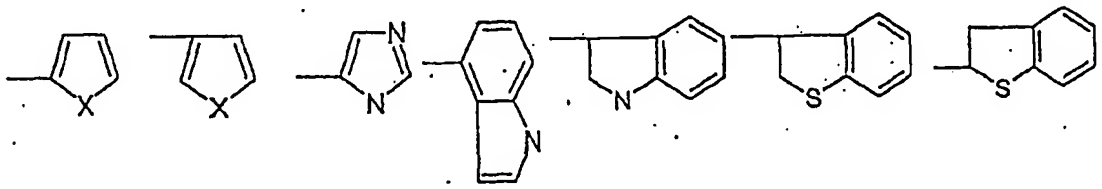
wherein

n is 1 to 5;

R2 is OA; R3 and R4 are each independently selected from H and OA; with A being selected from H, alkyl, alkoxymethyl or a group



wherein R6 and R7 are each independently alkyl, in particular C1-20 alkyl and particularly preferred C1-6 alkyl, or aryl, in particular optionally substituted phenyl;
R5 is a C1-3 alkyl;
R1 is a group selected from hydrogen, 3-pyridyl, 4-pyridyl, optionally substituted phenyl,

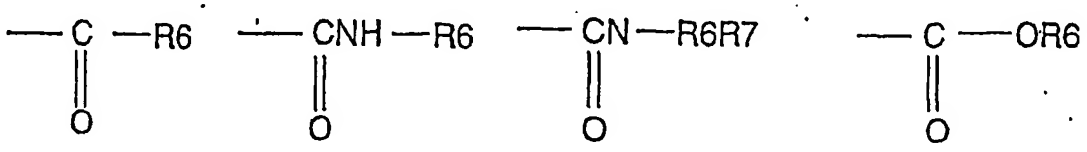


wherein X is selected from S, O or NH;

wherein the compound of formula I can be present as a racemate or as a pure (R)- or (S)-enantiomer,

as well as physiologically acceptable salts of these compounds, for the preventative treatment of Parkinson's disease, in particular for the prevention of dopaminergic cell loss in individuals in whom, before commencement of the preventive treatment, at least three of the four cardinal symptoms of the group bradykinesia, rigidity, resting tremors and postural instability are not yet present or are only rudimentary or partially present.

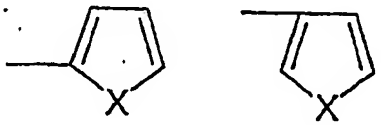
Compounds that are particularly suitable for the production of a neuroprotective agent or a prophylactic agent for Parkinson's disease are those in which R2 is an OA group and R3 and R4 are independently H or an OA group, it being particularly preferred for A to be a hydrogen atom or a group



in which R6 is a C1-20 alkyl, in particular C1-12 alkyl or C1-6 alkyl, phenyl or methoxyphenyl.

In another preferred embodiment of the invention R4 is H.
In another preferred embodiment of the invention R3 is H.
In another preferred embodiment of the invention R3 and R4 are both H.
In another preferred embodiment of the invention n = 1, 2 or 3, in particular n = 2 or 3.

R1 is preferably selected from the group H



und

wherein X is selected from S, O and NH and wherein it is especially preferred for X to be a sulphur atom.

It is especially preferred for R1 to be 2-thienyl.

In a further preferred embodiment of the invention, R5 is a C3-alkyl, in particular n-propyl.

In a further preferred embodiment of the invention, R1 is a 2-thienyl, R3 and R4 are both H, R5 is a C3 alkyl and n = 2.

In a particularly preferred embodiment of the invention, the racemate of (+/-) 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, and especially preferred the pure S-enantiomer of this compound (rotigotine), is used for the production of the prophylactic agent for Parkinson's disease.

The terms "C1-20 alkyl", "C1-12 alkyl" and "C1-3 alkyl" are each to be understood as branched or non-branched alkyl groups with the corresponding number of C-atoms. For example, a "C1-20 alkyl" includes all alkyls with 1 to 20 C-atoms. The alkyls can be optionally substituted, e.g. with halogen. The alkyls are preferably present in non-substituted form.

The term "alkoxymethyl" is to be understood as the group –CH2-O-alkyl. A preferred alkyl is a C1-12 alkyl, a C1-6 alkyl or a C1-3 alkyl.

The individuals to be prophylactically treated with the substituted 2-aminotetralines can be apparently healthy individuals, whose genetic or epidemic predisposition may not indicate an increased risk of developing Parkinson's disease.

In particular high-risk individuals or patients in whom early clinical, clinical/chemical or clinical/physical symptoms can be detected, but who, however, do not yet display two or more of the cardinal symptoms of Parkinson's disease, come into consideration for treatment with substituted 2-aminotetralines, in particular, rotigotine.

Finally, 2-aminotetralines, in particular rotigotine, can also be used as a neuroprotective agent if the diagnosis is not clear, but development of the symptoms towards Parkinson-like neurodegeneration can be expected.

Prevention of neuronal cell loss is required in particular by

(a) individuals with an increased risk of Parkinson's disease or
(b) individuals with early symptoms of Parkinson's disease.

The terms "Morbus Parkinson" and "Parkinson's disease" are used as synonyms in this patent application and include idiopathic and genetic Parkinson's disease. The so-called Parkinson-Plus syndrome as well as secondary Parkinsonism are to be differentiated therefrom.

The term "cardinal symptoms" of Parkinson's disease is to be understood in this patent application as one or more of the symptoms of bradykinesia, rigidity, resting tremors and postural instability.

"Individuals with an increased risk of Parkinson's disease" are to be understood in this patent application in particular as individuals who do not yet display any detectable symptoms of Parkinson's disease, but who have certain risk factors.

Such risk factors can be genetic mutations (Nussbaum NEJM 348, 2003, 25). For example, the parkin gene on chromosome 6q25.2-27 (PARK2) is associated with juvenile Parkinsonism and occurs more frequently in families with autosomal recessive Parkinson inheritance (Matsumine, Am. J. Hum. Genet., 60, 1997, 588; Kitada, Nature 392, 1998, 605; Abbas, Hum. Mol. Genet. 8, 1999, 567; Tassin, Am. J. Hum. Genet., 63, 1998, 88 und Lucking, N. Engl. J. Med. 342, 2000, 1560-7). Other gene loci, for example, PARK6 and PARK7, were also found with increased frequency in families with juvenile, recessively-inherited Parkinson's disease (Valente, Am. J. Hum. Genet. 68, 2001, 895;

van Dujin, Am. J. Hum. Genet. 69, 2001, 629). Mutations in the alpha-synuclein gene (PARK1) were detected in families with juvenile, autosomal dominantly-inherited Parkinson's disease (Polymeropoulos, Science 276, 1997, 2045). In addition to genetic predisposition, environmental influences, such as high exposure to, for example, insecticides (Vanacore, Neurol Sci., Sep; 23 Suppl 2, 2002, page 119) can also represent risk factors.

In this patent application, "individuals with early symptoms of Parkinson's disease" are to be understood in particular as individuals in whom at least three of the four cardinal symptoms (rigidity, resting tremors, bradykinesia and postural instability) are not yet present, or are only rudimentarily or partially present, but who manifest diagnostically useable early clinical, clinical/biochemical and/or clinical/physical symptoms.

Clinical/biochemical markers can be modifications in the alpha synuclein or neuromelanin pattern. Such modifications can be due, for instance, to the expression of genetic variants, for example of alpha synuclein, the development of aggregates or filaments, for example of alpha synuclein, or the increased release from cellular stores, for example, from the cytoplasms of cells that are being destroyed, as is the case with neuromelanin.

Early clinical/physical symptoms can be structural or functional changes to the brain, which can be physically detected, for example, by means of PET and SPECT studies, by means of transcranial sonography (Becker, J Neurol 249, Suppl 3, 2002, III/40; Prunier C, *et al.*, Neuroimage. 2003 Jul; 19(3): 810-6) or by detecting biochemical markers such as neuromelanin (WO 02/31499).

Early clinical symptoms can be olfactory disorders, depression, impairments of visual and cognitive functions or sleep disorders, whereby a combination of different tests can also be used for early diagnosis (Becker, J Neurol 249, Suppl 3, 2002, III/40; Stern, Annals of Neurol 56, 2004, 169).

As already discussed above, approximately 70 to 80% of the dopaminergic neurones of the substantia nigra have already been destroyed by the time at least two of the four cardinal symptoms have manifested themselves for the first time. In order to effectively use the surprising neuroprotective potential of the aminotetralines of formula I, in particular of rotigotine, the prophylactic treatment of the patients is therefore preferably initiated at a stage when the patients have a lower loss of dopaminergic cells of the substantia nigra (SN). Individuals displaying just one or none of the cardinal symptoms of Parkinson's disease in a clearly pronounced form are therefore preferably treated.

Individuals displaying a dopaminergic cell loss in the SN of less than 70%, 60%, 50% and particular preferred of less than 40%, 30%, 20% or 10% are preferably treated.

Two scores can be used as aids for diagnosing and controlling the therapy of patients already displaying noticeable motor disturbances, i.e. the UPDRS score and the Hoehn and Yahr score.

In a preferred aspect of the invention, the group of patients prophylactically treated with the aminotetralines of formula I, in particular with rotigotine, furthermore has a modified Hoehn and Yahr score of 0 to 2, particularly preferred of 0 to 1 and especially preferred of 0.

Table 2: Modified stage determination according to Hoehn, The natural history of Parkinson's disease in the pre-levodopa and post-levodopa eras. Neurologic Clinics 10, 1992, 331

Stage 0 = No sign of disease.
Stage 1 = Unilateral disease.
Stage 1.5 = Unilateral plus axial involvement.
Stage 2 = Bilateral disease without impairment of balance.
Stage 2.5 = Mild bilateral disease with recovery on pull test.
Stage 3 = Mild to moderate bilateral disease: slight postural instability; physically independent.
Stage 4 = Severe disability; still able to walk or stand unaided.
Stage 5 = Wheelchair-bound or bedridden unless aided

Patients with a UPDRS score, part III (see embodiment 5), of at least 10 are normally classified as patients who can be considered for dopaminergic therapy. However, the group of patients suitable for benefiting from the neuroprotective effect of substituted 2-aminotetralines of formula I, in particular rotigotine, preferably has a very low or undetectable motor UPDRS score (part III). Within the meaning of the present invention, the preventive treatment with substituted 2-aminotetralines of formula I, in particular with rotigotine, should therefore preferably be carried out on patients having a UPDRS motor score of less than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1. It is particularly preferred for the patients to still not display any motor disturbances at all.

The terms "prevention", "prophylaxis" and "preventive treatment" are used as synonyms in this patent application. They include, in particular, the administration of a medicament to individuals in whom at least three of the four cardinal symptoms of Parkinson's disease

(rigidity, resting tremors, bradykinesia, postural instability), are not yet present, or are only rudimentarily or partially present, in order to prevent or delay the appearance or significant development of the motor symptoms of Parkinson's disease and/or further dopaminergic neurone loss, particularly in the substantia nigra. The individuals to be prophylactically treated preferably do not yet display any of the cardinal symptoms in a distinctly pronounced form.

Compounds of formula I are optically active and can be present as racemates or as pure (R)- or (S)-enantiomers. In this patent application, the term "pure enantiomer" is understood to mean that a substance is preferably present to at least 90 mol% in the form of one enantiomer, e.g. in the (S) form, whilst the proportion of the respective other enantiomer, e.g. the (R) form, is correspondingly low. If, for example, rotigotine [(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] is used to produce the medicament according to the invention, the (R)-(+)-enantiomer is preferably present in a proportion of < 10 mol%, particularly preferred in a proportion of < 2 mol% and especially preferred in a mole proportion of < 1 %, based on the total amount of rotigotine in the prophylactic agent for Parkinson's disease.

Compounds of formula I can be present in the medicament as free bases or in the form of the physiologically acceptable salts, e.g. in the form of rotigotine hydrochloride.

"Physiologically acceptable salts" include non-toxic addition salts of a compound of formula (I) in the form of the free base, with organic or inorganic acids. Examples of inorganic acids include HCl.

There are many methods of application available for administering substituted 2-aminotetralines of formula I, in particular rotigotine, which the person skilled in the art can select and adapt depending on the need, condition and age of the patient, the required dosage and the desired application interval.

A preferred mode of administering substituted 2-aminotetralines of formula I, in particular rotigotine, is transdermal administration. The form of administration may, in principle, be selected from, for example, an ointment, a paste, a spray, a film, a plaster or an iontophoretic device.

Substituted 2-aminotetralines of formula I, in particular rotigotine, are preferably applied to the skin of the patient in plaster form, with the active substance preferably being present in a matrix of adhesive polymer, for instance a self-adhesive polysiloxane. Examples of suitable transdermal formulations can be found in WO 99/49852, WO

02/89777 and WO 02/89778. Such a form of administration enables a substantially constant plasma level to be established and therefore a constant dopaminergic stimulation over the entire application interval (WO 02/89778; Metman, Clinical Neuropharmacol. 24, 2001, 163).

If, on the other hand, a medicament in the form of a subcutaneous or intramuscular depot form is desired, substituted 2-aminotetralines of formula I, in particular rotigotine, may be suspended, for example as salt crystals, for instance as crystalline rotigotine hydrochloride, in a hydrophobic anhydrous medium and injected, such as described in WO 02/15903, or else administered in the form of microcapsules, microparticles or implants based on biodegradable polymers, such as described, for example, in WO 02/38646.

Other conceivable forms of administering substituted 2-aminotetralines of formula I, in particular rotigotine, are transmucosal formulations, for example sublingual sprays, rectal formulations or aerosols for pulmonary administration.

Suitable dosages of substituted 2-aminotetralines of formula I, in particular rotigotine, are between 0.05 and approximately 50 mg/day, with daily doses of preferably between 0.1 and 40 mg and in particular of between 0.2 and 20 mg/day being administered. Dosage can thereby take place in a gradually increasing manner, i.e. the treatment may optionally start with low doses which are then increased until the maintenance dose is reached.

It is clear to the person skilled in the art that the dosage interval may vary depending on the applied quantity, the mode of application and the daily requirement of the patient. Thus, a transdermal form of application may be designed, for example, for administration once a day, once every three days or once every seven days, whilst a subcutaneous or intramuscular depot can make it possible to administer injections, for example, in one-weekly, two-weekly or four-weekly cycles.

Other active substances which prevent the progression of dopaminergic cell loss can also be present in the neuroprotective medicament in addition to the substituted 2-aminotetralines of formula I, in particular in addition to rotigotine.

Examples hereof are substances with an anti-apoptotic effect (minocycline, FK-506, cyclosporine A, zVAD) as well as neurotrophins such as, for example, Glial-cell-derived neurotrophic factor (GDNF).

In a combination preparation, a sequential administration can be achieved, for example, in that an administration form, for example an oral tablet, has two different layers with differing release profiles for the different pharmaceutically active ingredients. It is clear to the person skilled in the art that various forms of administration and application patterns are conceivable within the context of the present invention, which all form subject matter of the invention.

A further subject matter of the application is a kit for the early diagnosis and treatment of Morbus Parkinson. Such a kit contains (a) a diagnostic agent that enables the diagnosis of Parkinson's disease and/or the predisposition to develop Parkinson's disease at an early or asymptomatic stage as well as (b) a pharmaceutical formulation containing substituted 2-aminotetralines of general formula I, in particular rotigotine.

Such a kit may comprise, for example:

(a) an agent or a diagnosis kit for detecting neuromelanin,
(b) a pharmaceutical formulation containing substituted 2-aminotetralines of general formula I, in particular rotigotine.

In another embodiment of the invention, the kit may contain:

(a) an agent or a diagnosis kit for detecting semaphorin 3,
(b) a pharmaceutical formulation containing substituted 2-aminotetralines of general formula I, in particular rotigotine.

In another embodiment of the invention, the kit may contain:

(c) an agent or a diagnosis kit for detecting alpha-synuclein and/or its aggregates,
(d) a pharmaceutical formulation containing substituted 2-aminotetralines of general formula I, in particular rotigotine.

In a further embodiment of the invention, the kit may contain:

(a) an agent or a diagnosis kit for genetically detecting a mutation associated with the appearance of Parkinson's disease and/or an allele associated with the more frequent appearance of Parkinson's disease, in particular, from the group of PARK genes 1, 2, 3, 4, 5, 6, 7 or 8 as well as the gene loci CYP2D6-B and GSTM1,
(b) a pharmaceutical formulation containing substituted 2-aminotetralines of general formula I, in particular rotigotine.

Embodiments:

Embodiment 1: Rotigotine Plaster

1.8 g of rotigotine (free base) were dissolved in 2.4 g of ethanol and added to 0.4 g of Kollidon 90F (dissolved in 1 g of ethanol). This mixture was added to a 74% solution of silicone polymers (8.9 g of BioPSA 7-4201 + 8.9 g of BIO-PSA 7-4301 [Dow Corning]) in heptane. Following the addition of 2.65 g of petrol ether, the mixture was stirred for 1 hour at 700 rpm in order to obtain a homogeneous dispersion. Following lamination on polyester, it was dried at 50°C. The final weight of the plaster was 50 g/cm2.

Embodiment 2: Rotigotine Depot Suspensions

(a) 1411.2 g of Miglyol 812 were weighed into a Duran flask. 14.4 g of Imwitor 312 were added to the Miglyol and then heated for 30 minutes to 80°C whilst being stirred. The clear solution was cooled to room temperature and filtered.

(b) 1188 g of the solution produced in (a) were transferred into a glass laboratory reactor, 12 g of N-0923 were added and homogenised for 10 minutes under nitrogen with an Ultraturrax at 10,000 rpm. The suspension was decanted into brown glass bottles whilst the Ultraturrax was running (2,000 rpm).

Embodiment 3: Sub-Acute MPTP Model

For the purpose of intoxication, 80 mg/kg of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) were administered to mice (in doses of 20 mg/kg at two-hour intervals, groups 3 to 6 in Figs. 1 and 2), which led to the degeneration of approximately 50 to 60% of the neurones of the substantia nigra (maximum degeneration in group 3 in Figs. 1 and 2). Rotigotine was administered daily for 7 days in doses of 0.3, 1 or 3 mg/kg respectively as the so-called "slow-release formulation" (see embodiment 2) (groups 4 to 6 in Figs. 1 and 2). A group of MPTP-treated animals (group 3) was given a rotigotine vehicle solution (see embodiment 2 without rotigotine HCl) and served as a reference. Groups 1, 2 and 7 served as controls, whereby group 1 did not receive any treatment at all, group 2 was treated with the vehicle solutions for MPTP and rotigotine and group 7 received exclusively rotigotine. The animals were killed on day 8 and their brains were removed and frozen. The frozen sections were incubated with 100 pm [^{125}I] PE2I ([^{125}I]-(E)-N(3-iodoprop-2-enyl)-2β-carboxymethyl-3β-(4'-methylphenyl)-nortropane) in phosphate buffer, pH 7.4, in order to mark the amount of dopamine transporters still present in the striatum, which indicates the number of functioning nerve endings. Rotigotine

improved the survival of the neurones and their nerve endings depending on the dosage. This is a clear indication of the neuroprotective properties of the substance (Figs. 1 and 2).

Embodiment 4: Acute MPTP Model (Including Apoptosis)

For the purpose of intoxication, 80 mg/kg of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) were administered to mice (in doses of 20 mg/kg at two-hour intervals), which led to the degeneration of approximately 50 to 60% of the neurones of the substantia nigra. Approximately 16 hours beforehand, rotigotine was administered in doses of 0.3, 1 or 3 mg/kg respectively, as the so-called "slow-release formulation". Diffusion and absorption latencies led to rotigotine then being optimally available when MPTP was administered. The animals were killed after 24 hours and their brains fixed. The brain sections were stained with FluoroJade to identify degenerating cells. The immunohistochemical marking of tyrosine-hydroxylase helped to identify dopaminergic neurones. The staining of tyrosine hydroxylase did not display any differences between the treated and untreated animals; staining with FluoroJade showed a large number of degenerating neurones; the neurones had, however, not yet been completely removed; this suggests that the cell destruction occurs apoptotically. The number of degenerating neurones was approximately 50% less following application of rotigotine, which further demonstrates the neuroprotective property of the substance (Table 1).

Embodiment 5: Determination of the Motor UPDRS Score

The motor UPDRS score (part III of the UPDRS score) is determined by examining the patient using criteria 18 to 31 as given below in Table 2, with the point scores resulting for each of the criterion being respectively added together.

Table 2:

III. MOTOR EXAMINATION

18. Speech:

☐ 0 - Normal.
☐ 1 - Slight loss of expression, diction and/or volume.
☐ 2 - Monotone, slurred but understandable; moderately impaired.
☐ 3 - Marked impairment, difficult to understand.
☐ 4 - Unintelligible.

19. Facial Expression:

☐ 0 - Normal.
☐ 1 - Minimal hypomimia, could be a normal "poker face".
☐ 2 - Slight but definitely abnormal diminution of facial expression.
☐ 3 - Moderate hypomimia; lips parted some of the time.
☐ 4 - Masked or fixed face with severe or complete loss of expression; lips parted by 7 mm.

20. Tremor at rest: (F = face, RH = right hand, LH = left hand, RF = right foot, LF = left foot)

F	RH	LH	RF	LF	
☐	☐	☐	☐	☐	0 - Absent.
☐	☐	☐	☐	☐	1 - Slight and infrequently present.
☐	☐	☐	☐	☐	2 - Mild in amplitude and persistent; or moderate in amplitude but only intermittently present.
☐	☐	☐	☐	☐	3 - Moderate in amplitude and present most of the time.
☐	☐	☐	☐	☐	4 - Marked in amplitude and present most of the time.

21. Action or Postural Tremor of the Hands: (R = right, L = left)

R	L	
☐	☐	0 - Absent.
☐	☐	1 - Slight; present with action.
☐	☐	2 - Moderate in amplitude, present with action.
☐	☐	3 - Moderate in amplitude, present with posture holding as well as action.
☐	☐	4 - Marked in amplitude; interferes with eating.

22. Rigidity: (Judged on passive movement of major joints on a patient in the sitting position. Cogwheeling can be ignored). (N = neck, RUE = right upper extremity, LUE = left upper extremity, RLE = right lower extremity, LLE = left lower extremity).

N	RUE	LUE	RLE	LLE	
☐	☐	☐	☐	☐	0 - Absent.
☐	☐	☐	☐	☐	1 - Slight or detectable only when activated by mirror-image or other movements.
☐	☐	☐	☐	☐	2 - Mild to moderate.
☐	☐	☐	☐	☐	3 - Marked, but full range of motion still achievable.
☐	☐	☐	☐	☐	4 - Severe, difficulty in carrying out all movements.

23. Finger Taps: (Patient taps thumb against index finger in rapid succession with maximum possible amplitude and separately with each hand). (R = right, L = left).

R L

☐ ☐ 0 - Normal.

☐ ☐ 1 - Slight slowing and/or reduction in amplitude.

☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.

☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.

☐ ☐ 4 - Can barely perform the task.

24. Hand Movements: (Patient opens and closes the hands in rapid succession with greatest possible amplitude and separately with each hand). (R = right, L = left).

R L

☐ ☐ 0 - Normal.

☐ ☐ 1 - Slight slowing and/or reduction in amplitude.

☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.

☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.

☐ ☐ 4 - Can barely perform the task.

25. Rapid Alternating Movements of the Hands: (pronation/supination movements of the hands, vertically or horizontally, with largest possible amplitude, both hands simultaneously).

R L

☐ ☐ 0 - Normal.

☐ ☐ 1 - Slight slowing and/or reduction in amplitude.

☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.

☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.

☐ ☐ 4 - Can barely perform the task.

26. Leg Agility: (Patient taps heel on the ground in rapid succession thereby lifting the entire leg. Amplitude should be at least 7.5 cm).

R L

☐ ☐ 0 - Normal.

☐ ☐ 1 - Slight slowing and/or reduction in amplitude.

☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.

☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.

☐ ☐ 4 - Can barely perform the task.

27. Rising from Chair: (Patient attempts to rise from a straight-back wooden or metal chair with arms folded across chest).

☐ 0 - Normal.

☐ 1 - Slow; may need more than one attempt.

☐ 2 - Pushes self up using arms of seat.

☐ 3 - Tends to fall back and may possibly have to make several attempts, but can rise without assistance.

☐ 4 - Unable to rise without assistance.

28. Posture:

☐ 0 - Normal erect.

☐ 1 - Not quite erect, slightly stooped posture; could be normal for an older person.

☐ 2 - Moderately stooped posture, definitely abnormal; can be leaning slightly to one side.

☐ 3 - Severely stooped posture with kyphosis; can be leaning moderately to one side.

☐ 4 - Marked flexion with extremely abnormal posture.

29. Gait:

☐ 0 - Normal.

☐ 1 - Walks slowly, may shuffle a few short steps, but no festination or propulsion.

☐ 2 - Walks with difficulty, but requires little or no assistance; possibly slight festination, short steps or propulsion.

☐ 3 - Severe disturbance of gait, requires assistance.

☐ 4 - Cannot walk at all, even with assistance.

30. Postural Stability: (Response to sudden rearwards displacement caused by pulling on the patient's shoulders whilst patient is erect and has their eyes open and feet slightly apart. Patient is prepared.)

☐ 0 - Normal.
☐ 1 - Retropulsion, but recovers unaided.
☐ 2 - No postural response; would fall if not caught by examiner.
☐ 3 - Very unstable, tends to lose balance spontaneously.
☐ 4 - Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia: (Combination of slowness, hesitancy, decreased arm-swing, small movement amplitude and poverty of movement in general.)

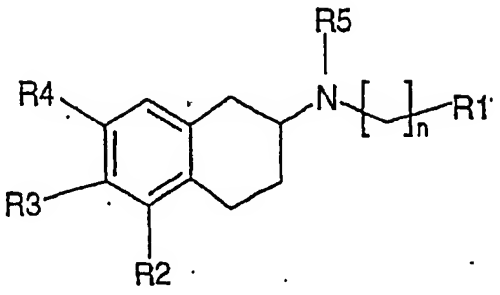
☐ 0 - None.
☐ 1 - Minimal slowing, movement is intentional; could be normal for some persons. Possibly reduced amplitude.
☐ 2 - Slight slowing and poverty of movement, which is clearly abnormal. Alternatively also reduced amplitude.
☐ 3 - Moderate slowing and poverty of movement or reduction in amplitude.
☐ 4 - Marked slowing, poverty of movement or reduction in amplitude.

Embodiment 6: In Vitro Conversion of a Prodrug into the Active Substance

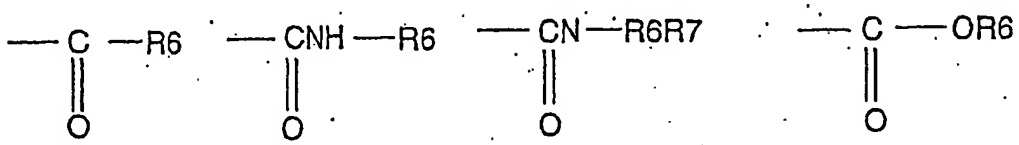
The microsome fraction that contains the essential metabolising enzymes is obtained from the liver cell homogenates of a human, monkey, dog, rat or mouse by means of differential centrifugation; the cytoplasmatic fraction can alternatively also be obtained. The subcellular fraction is suspended with a buffer such that a solution having a defined protein content is obtained. Following the addition of 1 µM of the prodrug to be tested, incubation takes place at 37°C for 60 min. Rotigotine is then quantified by means of HPLC/UV or also by means of HPLC/MS and is related to the used amount. The concentration or time series are examined for detailed analyses.

Patent Claims

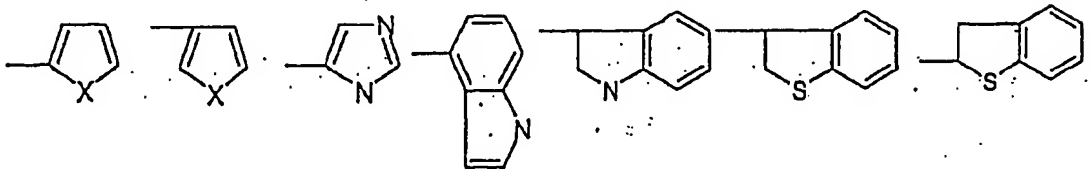
1. Use of a compound of the general formula I



wherein:
n = 1 to 5;
R2 is OA; R3 and R4 are each independently selected from H and OA; with A being selected from H, alkyl, alkoxymethyl or a group



wherein R6 and R7 are independently alkyl or aryl;
R5 is a C1-3 alkyl;
R1 is a group selected from hydrogen, 3-pyridyl, 4-pyridyl, optionally substituted phenyl,



wherein X is selected from S, O or NH;
wherein the compound of formula I is present as a racemate or as a pure (R)- or (S)-enantiomer;
as well as physiologically acceptable salts of these compounds, as a medicament for the preventative treatment of Parkinson's disease.

2. Use according to claim 1, wherein the preventative treatment is performed on individuals

who are selected from the group of

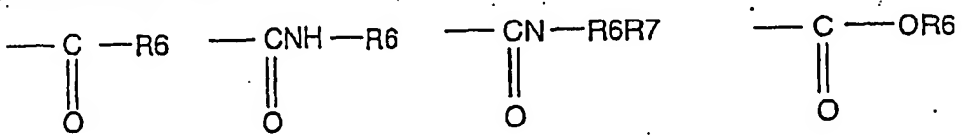
(a) individuals without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease or
(b) individuals with early symptoms of Parkinson's disease, in whom at least three of the four cardinal symptoms of Parkinson's disease (rigidity, resting tremors, bradykinesia, postural instability) are not yet or are only partially present.

3. Use according to claim 2, wherein the individuals described in point (b) display several of the following clinical symptoms: olfactory disorders, depression, sleep disorders of the type "REM behaviour disorder", constipation and short-term movement anomalies.

4. Use according to claim 2, wherein the individuals display a mutation in a PARK gene and/or modifications to the alpha synuclein or neuromelanin pattern.

5. Use according to one of the preceding claims, wherein R3 and R4 each represent hydrogen.

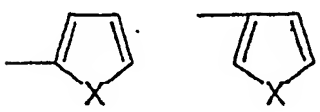
6. Use according to one of the preceding claims, wherein A is a hydrogen atom or a group selected from



wherein R6 is C1-12 alkyl, phenyl or methoxyphenol.

7. Use according to one of the preceding claims, wherein n = 1 to 3.

8. Use according to one of the preceding claims, wherein R1 is selected from the group



und

wherein X is S, O or NH.

9. Use according to one of the preceding claims, wherein X is a sulphur atom.

10. Use according to one of the preceding claims, wherein R5 is a C3 alkyl.

11. Use according to one of the preceding claims, wherein R1 is a 2-thienyl, R3 and R4 are both H, R5 is a C3 alkyl and n = 2.

12. Use according to one of the preceding claims, wherein the compound is 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol.

13. Use according to claim 12, wherein the compound is the pure S-enantiomer (rotigotine).

14. Use according to one of the preceding claims, wherein the individuals display a dopaminergic cell loss in the substantia nigra of less than 60% before commencement of medicament administration.

15. Use according to one of the preceding claims, wherein the individuals have a UPDRS score of less than 10 before commencement of medicament administration.

16. Use according to one of the preceding claims, wherein the individuals have a Hoehn-Yahr score of 0 or 1.

17. Use according to one of the preceding claims, wherein the medicament is provided for parenteral, transdermal or mucosal administration.

18. Use according to one of the preceding claims, wherein the compound of general formula I is administered in a dose of 0.05 to 50 mg per day.

19. Kit for the diagnosis and treatment of Parkinson's disease, comprising

(a) a diagnostic agent that enables the diagnosis of Parkinson's disease and/or the predisposition to develop Parkinson's disease at an early or asymptomatic stage and
(b) a pharmaceutical formulation comprising substituted 2-aminotetralines of general formula I, as defined in one of claims 1 to 13.

20. Kit according to claim 19, wherein the diagnostic agent (a) is selected from:

(i) an agent or a diagnosis kit for detecting neuromelanin
(ii) an agent or a diagnosis kit for detecting semaphorin 3
(iii) an agent or a diagnosis kit for detecting alpha-synuclein and/or its aggregates or
(iv) an agent or a diagnosis kit for genetically detecting a mutation associated with the appearance of Parkinson's disease and/or an allele associated with the more frequent appearance of Parkinson's disease.

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Figures: 1+2

Pages:

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(54) (S)-2-N-PROPYLAMINO-5-HYDROXYTETRALINE UTILISEE COMME AGENT THERAPEUTIQUE AYANT UN EFFET AGONISTE SUR LE RECEPTEUR D3

(54) (S)-2-N-PROPYLAMINO-5-HYDROXYTETRALIN AS A D3-AGONIST

(57)

The invention relates to a medicament containing (S)-2-N-propylamino-5- hydroxytetralin, the salts or prodrugs thereof. As a D3 agonist, (S)-2-N- propylamino-5-hydroxytetralin is suitable particularly for the treatment of dopa-sensitive movement disorders.

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(54) Titre : (S)-2-N-PROPYLAMINO-5-HYDROXYTETRALINE UTILISEE COMME AGENT THERAPEUTIQUE AYANT UN EFFET AGONISTE SUR LE RECEPTEUR D3

(54) Title: (S)-2-N-PROPYLAMINO-5-HYDROXYTETRALIN AS A D3-AGONIST

(57) Abrégé/Abstract:
The invention relates to a medicament containing (S)-2-N-propylamino-5-hydroxytetralin, the salts or prodrugs thereof. As a D3 agonist, (S)-2-N-propylamino-5-hydroxytetralin is suitable particularly for the treatment of dopa-sensitive movement disorders.

ABSTRACT

The invention relates to a medicament containing (S)-2-N-propylamino-5-hydroxytetralin, the salts or prodrugs thereof. As a D3 agonist, (S)-2-N-propylamino-5-hydroxytetralin is suitable particularly for the treatment of dopa-sensitive movement disorders.

Translation
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(S)-2-N-propylamino-5-hydroxytetralin as a D3 agonist

Dopamine is an essential neurotransmitter of the central nervous system. The activity of dopamine is mediated via the binding to five different dopamine receptors. These receptors can be arranged by their morphology and their manner of signal transduction into classes "D1-like" (D1 and D5) as well as "D2-like" (D2, D3 and D4 receptors).

The D3 receptor was first cloned by Sokoloff (Nature 347, 1990, 146) and is especially expressed in the limbic system, in which emotional and cognitive processes are controlled. It is also somewhat less pronounced in the striatal motor tissue where it serves the purpose of fine regulation of movement processes (Joyce, Pharmacol. Ther. 90, 2001, 231-259). Recently the D3 receptor has been considered as a promising target for the development of active agents for the treatment of different psychiatric and motor diseases.

Consequently, D3 agonists could represent valuable therapeutics for the treatment of different types of depression, anxiety disorders, sexual dysfunctions, glaucoma, cognitive disorders, restless leg syndrome, attention deficit hyperactivity syndrome (ADHS), hyperprolactinemia, hyperprolactinome, eating disorders, Parkinson associated movement disorders, DOPA and neuroleptica induced movement disorders, e.g. akathisia, rigor, dystonia and dyskinesia, as well as cocaine, alcohol, opiate and nicotine addiction, galacthorrhoe and acromegaly.

Further, D3 agonists have neuroprotective potential for the treatment and prophylaxis of neurodegenerative disorders (Pulverenti, L. et al, Trends Pharmacol. Sci. 2002, 23, 151-153; Joyce, Pharmacology and Therapeutics 90, 2001, 231; EP 988 296; WO 03/29233; WO 93/23035).

Thus, there is a need for high affinity D3 agonists with preferably greater functional selectivity as compared to "D1-like" receptors and with significant selectivity as compared to the remaining "D2-like" receptors.

It was surprisingly found that (S)-2-N-propylamino-5-hydroxytetralin has the desired characteristics.

Racemic 2-N-propylamino-5-hydroxytetralin is known from the literature.

Hacksell et al (J. Med. Chem. 22, 1979, 1469) evaluated different N-alkylated 2-aminotetralins in regard to their dopamine receptor stimulating activity. A particular dopaminergic activity was demonstrated for the racemic 2-N-propylamino-5-hydrotetralin. However, the agonistic activity of the substance with an ED_{50} of 40 nM/kg is only moderate and the AUC and the half life are short in comparison to the other evaluated compounds. It was found that aminotetralins with N,N-dialkylation were the most active and appropriate compound for the intended oral administration.

Beaulieu et al (Eur. J. Pharmacol. 105, 1984, 15) evaluated N,N-disubstituted 2-aminotetralin in regard to its D2 stimulating activity. The racemic 2-N-propylamino-5-hydroxytetralin demonstrated a moderate activity while N,N-dialkylated 2-amino-5-hydroxy derivate, like N-0437 (racemic rotigotine), showed a significantly higher activity. Conclusions to possible therapeutic potential of 2-N-propylamino-5-hydroxytetralin were not made.

Seiler et al (J. Med. Chem. 29, 1986, 912) disclose 2-N-propylamino-5-hydroxytetralin as an educt for syntheses of N-dialkylated compounds. A biological activity of 2-N-propylamino-5-hydroxytetralin is not described.

Swart et al (Toxicology Methods 3, 1993, 279) describe the racemate of 2-N-propylamino-5-hydroxytetralin as rotigotine metabolite with weaker dopaminergic activity. Rotigotine [5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthalenol] is an example of a dopamine receptor agonist with D2/D3 agonistic activity. In comparison to rotigotine, which binds with a K_d value of 5 nM to a dopamine receptor rich membrane fraction, 2-N-propylamino-5-hydroxytetralin demonstrates a clearly higher K_d value of 1.3 µM. The authors come to the conclusion that the N-dealkylated metabolites of rotigotine have a dopaminergic activity too weak for them to have a therapeutic relevance.

Swart et al (J. Analytical Toxicology 18, 1994, 71) disclose the (S)-enantiomer of 2-N-propylamino-5-hydroxytetralin as a metabolite of rotigotine. A biological activity is not described.

Sonesson et al (J. Med. Chem. 38, 1995, 1319) evaluated the biological activity of monopropyl analogue of {[(trifluormethyl)sulfonyl]oxy}-2-aminotetralins. The enantiomers of 2-N-propylamino-5-hydroxytetralin were disclosed as intermediate synthesis products, however they were not biologically characterized.

EP 026 848, EP 717 620, WO 94/26703 and WO 01/38321 disclose 2-N-propylamino-5-hydroxytetralin as an educt for the synthesis of N-dialkylated and sulfonated aminotetralin. The medical application of 2-N-propylamino-5-hydroxytetralin is not suggested.

Van Vliet et al (J. Med. Chem. 39, 1996, 4233) evaluate the applicability of competition tests with D2L agonists and D2L antagonists for the prediction of dopamine receptor subtype selectivity. Here aminotetralin is evaluated in regard to its D3 selectivity and potential suitability as antipsychotic. Within the scope of this evaluation, racemic 2-N-propylamino-5-hydroxytetralin was applied as well as 27 other substances. Functional data for (ant)agonistic activity of the used substances was not collected. The medical use of 2-N-propylamino-5-hydroxytetralin is not suggested. On the other hand, the authors come to the conclusion on page 4236 that, with the exception of compound (+)25, that none of the applied substances demonstrate the desired pharmacological profile of a D3 selective antipsychotic.

In summary, the racemic 2-N-propylamino-5-hydroxytetralin is, from the state of the art, known as an unselective, moderately active dopamine agonist with a modest half life. Even though a known dopaminergic activity of the racemic 2-N-propylamino-5-hydroxytetralin has been known since 1969 (see Hacksell et al, supra), a medical use of this substance is not described and is also not suggested. On the contrary, Swart et al come to the conclusion that the N-dealkylated metabolites of rotigotine have a dopaminergic activity which is too weak to be therapeutically relevant (Tox. Meth. 3, 1993, page 289, last paragraph).

Consequently, there was no motivation for the skilled person to consider an enantiomeric separation of this obviously therapeutically unsuitable substance and to test the individual enantiomers for their therapeutic potential.

It was therefore surprising that the pure (S)-enantiomer of 2-N-propylamino-5-hydroxytetralin demonstrated a particular affinity to and a noticeable functional selectivity for the D3 receptor as well as a pure agonistic activity, which made the substance a valuable candidate for the treatment of diseases caused by dopamine deficiency. This therapeutically attractive profile of the pure (S)-enantiomer was not identified in the previous studies with 2-N-propylamino-5-hydroxytetralin.

As a matter of fact, the (S)-enantiomer of 2-N-propylamino-5-hydroxytetralin in fact binds with a Ki value of 7.6 nM to the D3 receptor. In comparison, the binding compared to other dopamine receptor subtypes is considerably less pronounced. Overall the receptor binding tests demonstrate a selectivity D3/D1 and D3/D5 of >1000 and of D3/D2 of approx. 40 (Table 1).

Table 1

IC_{50} value of (S)-2-N-propylamino-5-hydroxytetralin to receptor subtypes

Receptor	Ki [nM]
dopamine D1 (h)	>10000
dopamine D2S (h)	290
dopamine D3 (h)	7,6
dopamine D4.2 (h)	30
dopamine D4.4 (h)	27
dopamine D4.7 (h)	46
dopamine D5 (h)	2000

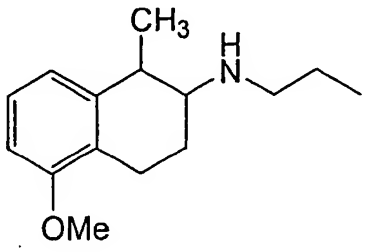
Further, it was found in functional tests that the activity of (S)-2-N-propylamino-5-hydroxytetralin is purely agonistic, and a strongly pronounced functional D3 selectivity is present in comparison to the D1 receptor as well as a significant selectivity in comparison to the D2 receptor (Table 2).

Table 2

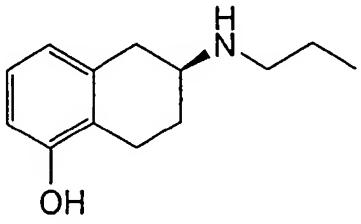
EC_{50} value of (S)-2-N-propylamino-5-hydroxytetralin to receptor subtypes

Receptor Subtype	EC_{50} (nM)
D1	1129
D2L	2.7
D3	0.67
D4.4	23.4
D5	1310

In comparison to (S)-2-N-propylamino-5-hydroxytetralin the structurally very similar compounds AJ76 and UH232 (Hacking and Stark, ChemBioChem 2002, 947) demonstrate a reduced D3 preference. Moreover, it was surprisingly determined that (S)-2-N-propylamino-5-hydroxytetralin has D2/D3 agonistic activity, while the structurally closely related AJ76 is described as a pure antagonist. The resulting therapeutic profile of (S)-2-N-propylamino-5-hydroxytetralin differs considerably from that of the structurally similar AJ76.



AJ76



(S)-2-N-propylamino-5-hydroxytetralin

In comparison to rotigotine, from which the (S)-2-N-propylamino-5-hydroxytetralin in minimal amounts metabolically emerges, (S)-2-N-propylamino-5-hydroxytetralin shows the same agonistic effectivity (EC_{50}) to D3 receptor, but 564 times and 385 times less affinity to D1 and D5 receptor, respectively, and subsequently a higher selectivity for D3 in comparison to these receptors.

Consequently, an aminotetralin as high affinity D3 agonist with great functional selectivity in comparison to dopaminergic D1 and D5 receptors, considerable selectivity to D4.4 receptor and significant selectivity in comparison to D2L receptor is provided with (S)-2-N-propylamino-5-hydroxytetralin for the therapy of diseases which respond to a therapy by dopamine or dopamine agonists.

A subject matter of the present invention is thus a pharmaceutical composition comprising 2-N-propylamino-5-hydroxytetralin or its pharmaceutically acceptable salts and prodrugs thereof, wherein 2-N-propylamino-5-hydroxytetralin is preferred as a pure (S)-enantiomer.

In regard to the term "pure (S)-enantiomer" it is understood in this invention that the amount of (R)-enantiomer in the medicament is preferred with an amount of < 10 mol%, more preferably with an amount of < 2 mol% and most preferred with a mol amount of < 1 % in regard to the total amount of 2-N-propylamino-5-hydroxytetralin in the pharmaceutical composition.

The term "pharmaceutically acceptable salts" encompasses in particular non-toxic addition salts of 2-N-propylamino-5-hydroxytetralin with organic or inorganic acids as well as their hydrates and solvates. Examples for inorganic acids comprise HCl, HBr, sulfuric acid, sulfurous acid, phosphorous acid and phosphoric acid. Organic acids comprise acetic acid, propionic acid, pyruvic acid, butyric acid, α-, β- or γ-hydroxybutyric acid, valeric acid, hydroxyvaleric acid, capronic acid, hydroxycapronic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, glycolic acid, lactic acid, D-glucuronic acid, L-glucuronic acid, D-galacturonic acid, glycine, benzoic acid, hydroxybenzoic acid, gallic acid, salicylic acid, vanillic acid, coumarinic acid, caffeic acid, hippuric acid, orotic acid, L-tartaric acid, D-tartaric acid, D,L-tartaric acid, meso-tartaric acid, fumaric acid, L-malic acid, D-malic acid, D,L-malic acid, oxalic acid, malonic acid, succinic acid, maleic acid, oxalic acetic acid, glutaric acid, hydroxyglutaric acid, ketoglutaric acid, adipinic acid, ketoadipinic acid, pimelic acid, glutamic acid, asparaginic acid, phthalic acid, propanetricarboxylic acid, citric acid, isocitric acid, methanesulfonic acid, toluene sulfonic acid und trifluoromethanesulfonic acid.

In this patent application the term "prodrug" of (S)-2-N-propylamino-5-hydroxytetralin describes in particular compounds understood which, in the human body, particularly in plasma or during entry through the skin or mucosa in therapeutically effective amounts, are cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin, whereby in this patent application rotigotine as prodrug of 2-N-propylamino-5-hydroxytetralin is excluded.

As prodrugs, in particularly derivatives of phenolic hydroxy groups, e.g. ester, carbonates, acetals, ketals, phosphates, phosphonates, sulphates, sulphonates, carbamates and silyl ethers come into question. Especially preferred prodrugs are esters and carbamates.

Other prodrugs can be easily enzymatically cleavable, hydrolysable or unstable derivatives of the amino function of (S)-2-N-propylamino-5-hydroxytetralin, e.g. amides, carbonates or hydroxylamines. N,N-dialkyl derivatives, as e.g. the rotigotine or (S)-2-N-propylamino-5-hydroxytetralin, are on account of their stability not prodrugs in the sense of the present patent application.

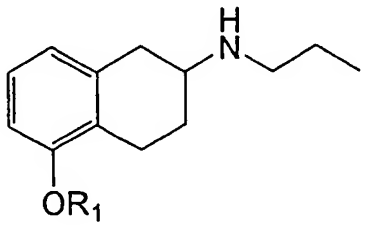
The preparation of (S)-2-N-propylamino-5-hydroxytetralin can be conducted as described in the literature (see Hacksell et al, J. Med. Chem. 22, 1979, 1469; Sonesson, J. Med. Chem. 38, 1995, 1319, US 5,442,117). The production of prodrugs via reaction of 2-N-propylamino-5-hydroxytetralin with appropriate reactive precursors like acid chlorides, acid anhydrides, carbamoyl chlorides, sulfonyl chlorides etc. is known to the skilled person in the field of clinical chemistry. Corresponding protocols are obtainable from the relevant literature. Examples for literature citations for the production of prodrugs are Bundgaard: Design of Prodrugs, Elsevier, Amsterdam, 1985; Higuchi and Stella: Pro-drugs as novel drug delivery stems in American Chemical Society, Washington DC, 1975; Sloan: Prodrugs - Topical and Ocular Drug Delivery, Ed: M. Dekker, 1992; Roche: Design of biopharmaceutical properties through prodrugs and analogs, Washington DC, 1977.

The basic suitability of 2-N-propylamino-5-hydroxytetralin derivative as prodrug can for example be determined by incubating the respective compounds under defined conditions with an enzyme cocktail, a cell homogenisate or an enzyme-containing cell fraction and measuring the resulting 2-N-propylamino-5-hydroxytetralin. A suitable enzyme mix is for example included in the S 9 liver preparation of the Gentest Company, Woburn, Ma, USA.

Alternatively, an incubation with fresh blood or plasma or a homogenate of the dermis can follow, in order to demonstrate a liver independent metabolism of the prodrugs as active components. For transdermal application an in vitro evaluation of permeation on excized skin is required. The final verification of the suitability and potential activity in the disease models is carried out by a measurement of the 2-N-propylamino-5-hydroxytetralin formed from the prodrug in plasma.

In vivo a prodrug should release enough (S)-2-N-propylamino-5-hydroxytetralin that a therapeutically effective steady-state concentration of (S)-2-N-propylamino-5-hydroxytetralin is achieved in plasma. In general, concentrations of (S)-2-N-propylamino-5-hydroxytetralin between 0.02 and 100 ng/ml, preferably between 0.05 ng and 50 ng/ml and most preferably between 0.1 and 40 ng/ml plasma are considered therapeutically effective concentrations.

A further embodiment of the invention is a pharmaceutical composition comprising a prodrug of the general formula I:



wherein R1 is selected from the group consisting of alkyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acetal, ketal, -C(O)NR2R3, -C(O)NHR2, $-S(O)_2R2$, $-S(O)_2OR2$, $-P(O_2H)OR2$, $-P(O_2H)R2$,

wherein R2 and R3 are respectively selected from H, C1-6-alkyl, C3-10-cycloalkyl, benzyl or phenyl, and wherein a compound of formula I is present as a pure (S)-enantiomer.

Preferably R1 is selected from the group of C1-6-alkylcarbonyl, C3-10-cycloalkylcarbonyl, benzoyl, -C(O)NR2R3 and -C(O)NHR2.

"Alkyl" can be either a branched or unbranched alkyl group which preferably has 1 to 10 C-atoms, more preferably 1 to 6 C-atoms and most preferably 1, 2 or 3 C-atoms, e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, s-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, t-pentyl, 1-methylbutyl, 2-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl and n-hexyl. Alkyl groups can additionally be substituted with one or more substituents, for example with halogen.

"Cycloalkyl" is an alkyl group which may consist only of ring-forming C-atoms or can optionally further carry branched C-atoms. Preferred chain lengths are 3-10, more preferred 4-8 or 4-6 C-atoms.

"Alkoxy" is the group -O-alkyl, wherein alkyl is preferably selected from the above mentioned groups for "alkyl". Preferred as alkyloxy is a C1-6-alkoxy group, more preferred is a C1-3-alkyloxy group.

"Aryl" is preferably phenyl. Phenyl can be, where appropriate, additionally substituted in one or more positions, e.g. with alkoxy, alkyl, halogen or nitro.

"Aralkyl" is the group -alkyl-aryl, wherein alkyl and aryl are preferably selected from the above mentioned groups "alkyl" respectively "aryl". "Aralkyl" is preferably benzyl.

"Acyl" encompasses in particular the groups -C(O)-alkyl ("alkylcarbonyl"), -C(O)-cycloalkyl ("cycloalkylcarbonyl"), -C(O)-aryl ("arylcarbonyl") and C(O)-alkyl-aryl ("aralkylcarbonyl"), wherein "alkyl", "cycloalkyl", "aryl" and "aralkyl" are preferably selected from the above-mentioned groups for "alkyl", "cycloalkyl", "aryl" and "aralkyl", whereby -C(O)-C1-6-alkyl and C(O)-phenyl are most preferred. Acyl is for example acetyl, propionyl, butyryl or -C(O)-phenyl ("benzoyl").

"Alkoxycarbonyl" is the group -C(O)-O-alkyl, wherein "alkyl" is preferably selected from the above-mentioned group "alkyl". Alkoxycarbonyl is preferably a C1-6-alkoxycarbonyl group.

"Cycloalkoxycarbonyl" is the group -C(O)-O-cycloalkyl, wherein "cycloalkyl" is preferably selected from the above-mentioned "cycloalkyl" groups.

"Aryloxycarbonyl" is the group -C(O)-O-aryl, wherein "aryl" is preferably selected from the above-mentioned "aryl" groups.

"Aralkoxycarbonyl" is the group -C(O)-O-aralkyl, wherein "aralkyl" is preferably selected from the above-mentioned "aralkyl" groups.

"Ketal" is in particular the group -CR'R"-O-alkyl or -CR'R"-O-aryl bound to the phenolic oxygen atom, wherein "alkyl" and "aryl" are preferably selected from the above-mentioned groups "alkyl" and "aryl", and wherein R' and R" independently represent

alkyl or aryl groups. "Acetal" differs from "ketal" in that the substituent R' in acetal is a hydrogen.

"Halogen" is preferably fluorine, chorine, bromine or iodine.

A further embodiment of the invention is the use of 2-N-propylamino-5-hydroxytetralin, in particular as pure (S)-enantiomer, or the salts or prodrugs thereof for the preparation of a medicament for the treatment or prophylaxis of a disease selected from the group of cocaine-, alcohol-, opiate- and nicotine addiction; neurodegenerative disorders, in particular Morbus Parkinson; sexual dysfunctions, in particular male erectile dysfunction; depression, in particular endogenous monophasic depression ("major depression"); hyperprolactinemia; hyperprolactinoma; glaucoma; cognitive disorders; restless leg syndrome; attention deficit hyperactivity syndrome (ADHS); galactorrhoe; acromegaly; Parkinson associated movement disorders, e.g. rigor, dystonia and dyskinesia; L-DOPA-induced disorders, idiophatic dystonia, in particular Segawa-syndrome; neuroleptica induced (tardive) dyskinesia, dystonia and akathisia as well as Parkinson plus syndrome.

In this patent application, under the term "opiates" both naturally occuring opiates, like morphin, as well as synthetic opiates, like heroin, are subsumed.

Further, the medicaments can be used for drug-supported ablactation after pregnancy.

In particular the compounds according to the invention are suitable for the manufacture of medicament for treating L-DOPA-sensitive movement disorders. Such movement disorders could be for example dyskinesia, dystonia, rigor and tremor. It is understood by the term "L-DOPA-sensitive" that the movement disorder can be advantageously influenced via administration of medicaments, which influence the dopaminergic signal transduction. One typical example for this is the Segawa-syndrome, an idiopathic dystonia, by which the use of L-DOPA as diagnostic criteria can be used. Other examples for L-DOPA-sensitive disorders are Morbus Parkinson associated, or L-DOPA or neuroleptica-induced movement disorders as well as the restless leg syndrome.

Morbus Parkinson, associated or L-DOPA or neuroleptica-induced movement disorders are for example dyskinesias, dystonias und walking disorders ("freezing"). With the use of L-DOPA therapy, the so-called "wearing off" phenomenon regularly appears, which means a loss of activity of L-DOPA, which can be mitigated or slowed through the use of monotherapy or combined therapy with suitable D3 dopamine agonists.

A preferred use of (S)-2-N-propylamino-5-hydroxytetralin thus relates to the manufacture of a medicament for the treatment of movement disorders, such as dyskinesias, dystonias and walking disorders, which spontaneously appear in the process of Parkinson diseases, but which may also be induced by medication. Included in the medication-induced movement disorders, like dyskinesias and dystonias, are particularly those which are induced via L-DOPA or dopamine antagonists.

Finally, the pharmaceutical compositions according to the invention can also be provided, independent from the diseases to be treated, as a combination preparation for simultaneous or sequential application.

For example, a unit to be sold which comprises a medication for treatment of Parkinson's disease comprising L-DOPA, can also encompass a pharmaceutical composition which comprises (S)-2-N-propylamino-5-hydroxytetralin or pharmaceutically acceptable salts and prodrugs thereof. In this case L-DOPA and the compounds according to the invention can be present in the same pharmaceutical formulation, e.g. in a combination tablet, or also in different application units, e.g. in the form of two separate tablets or in two different application forms, e.g. as oral L-DOPA medication and as transdermal or transmucosal (S)-2-N-propylamino-5-hydroxytetralin formulation. As according to the need, both active agents can be applied simultaneously or separately over time.

In a combination preparation, a sequential dose can be for example achieved by providing an administration form, e.g. an oral tablet, having two different layers with differing release profiles for the different pharmaceutically active components. It is clear to the skilled person that in the context of the current invention different administration forms and application schedules are possible, all of which are subject-matter of the invention.

An embodiment of the invention therefore relates to a medicament which comprises L-DOPA or a neuroleptic agent like (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt and prodrug thereof for simultaneous or sequential application to patients.

Typically, the medicaments of the current invention consist of a pharmaceutical composition which comprises, in addition to (S)-2-N-propylamino-5-hydroxytetralin or the pharmaceutically acceptable salts and prodrugs thereof, at least one pharmaceutically acceptable carrier or adjuvant.

The pharmaceutical formulation can be differently formulated, independently of the intended manner of application. Thus the pharmaceutical formulation can for example be adjusted for intravenous, intramuscular, intracutaneous, subcutaneous, oral, buccal, sublingual, nasal, transdermal, inhalative, rectal or intraperitoneal application.

The respective formulations and the suitable pharmaceutical carriers or adjuvants for this purpose, like fillers, disintegrants, binders, lubricants, stabilizers, flavors, anti-oxidants, preservatives, dispersants or solvents, buffers or electrolytes, are known to the person skilled in the art in the field of pharmaceutics, and are for example described in standard works like Sucker, Fuchs and Speiser ("Pharmazeutische Technologie", Deutscher Apotheker Verlag, 1991) and Remington ("The Science and Practice of Pharmacy", Lipponcott, Williams & Wilkins, 2000).

In one embodiment of the invention, the pharmaceutical compositions which comprise the compounds according to the invention are administered orally and can be present in the form of for example capsules, tablets, powders, granulates, coated tablets or in a liquid form.

At the same time, the formulation can be in the form of a fast release application, when a rapid onset of the effect is desired. Respective oral formulations are for example described in EP 0 548 356 or EP 1 126 821.

Suitable formulations for fast release of (S)-2-N-propylamino-5-hydroxytetralin or pharmaceutically acceptable salts and prodrugs thereof are in particular formulations for mucosal application, for example buccal or sublingual dosage forms or nasal sprays. These formulations are an ideal way to quickly counterbalance the "lows" of L-DOPA-concentration which are associated with L-DOPA therapy and to treat the movement disorders associated with the "off-phases" of L-DOPA therapies e.g. akinesias.

The transmucosal formulation can be in either a solid or liquid form. Solid mucosal application forms are for example quickly disintegrating sublingual tablets or muco-adhesive application forms. Preferred are liquid formulations which are suitable for use as a spray, in particular as a nasal spray.

A mucosal formulation in spray form can be in the simplest form an active ingredient solution. This can, if appropriate, be made isotonic with the addition of suitable

electrolytes, e.g. sodium chloride or dextrose. A transmucosal spray of (S)-2-N-propylamino-5-hydroxytetralin or a prodrug thereof can for example be an aqueous solution, a solution in non-aqueous solvents, such as oils, glycerol or propylenglycol, or an emulsion. Further, such a transmucosal formulation can comprise buffers usual in the pharmaceutical art to adjust the desired pH of the active agent solution. Advantageously, the pH of a transmucosal formulation is set in a manner that the mucous membranes are not irritated during the application of the formulation. This is with nasal application usually with a mild acidic pH in the range between 3 and 6 the case. Suitable buffers are for example acetate, citrate and phosphate buffers. Further, additional adjuvants can be present in the transmucosal formulation, e.g. in the nasal spray, as e.g. solubilizers, penetration improvers, preservatives, antioxidants, thickeners and additives for improvement of taste.

On the other hand, if a protracted release is desired, a formulation with sustained release of the active agent may be used. Respective oral and non-oral formulations are likewise known from the state of the art.

For example, (S)-2-N-propylamino-5-hydroxytetralin or the salts or prodrugs thereof may be applied in the form of patches to the skin of the patient, wherein the active agent is preferably in a matrix of adhesive polymer, e.g. a self-sticking polysiloxane adhesive. Examples for transdermal formulations are found in WO 99/49852, WO 02/89777, WO 02/89778 and WO 2004/012721. Such an administration form provides for adjusting an essentially constant plasma level and therewith a constant dopaminergic stimulation during the entire interval of application (WO 02/89778; Metman, Clinical Neuropharmacol. 24, 2001, 163).

On the other hand, if a medicament in the form of a subcutaneous or intramuscular depot form is desired, (S)-2-N-propylamino-5-hydroxytetralin, or the salts or prodrugs thereof can be suspended and injected, for example, as salt crystals, e.g. as crystalline hydrochloride, in a hydrophobic water-free medium. An example formulation is described in WO 02/15903.

Alternative pharmaceutical preparations can be for example infusion or injection solutions, oils, suppositories, aerosols, sprays, patches, microcapsules or microparticles.

Examples

1. Determination of receptor affinities

The receptor affinities were measured using competition experiments. For this purpose the receptors are incubated with radio-labelled receptor-specific ligands. Primarily, human receptors are used which are expressed in cell lines. Alternatively, membrane preparations from rat or bovine brains are used. The incubation conditions are published and standardized. Differing concentrations of the substance ((S)-2-N-propylamino-5-hydroxytetralin) to be tested are added to the incubation preparations, in order that a dose-binding curve can be established. Unspecific binding is separated from specific binding through incubation with unspecific ligands. The proportion of specific binding in different substance concentrations is represented in % of the maximum binding of the ligand. The IC50 value (concentration at 50 % inhibition of the binding to the ligand) and the slope are determined with regression analysis. Using the Cheng-Prusoff-equation, the Ki value is determined, which then is used for comparison: the lower the Ki value, the higher the affinity (see Table 1).

2. Determination of functional characteristics

In order to measure the intrinsic activity of the substance, human dopamine receptors were functionally expressed in cell lines (CHO-DUKX-SRE or SH-SY5Y-SRE). That means that after binding of agonists an intracellular signal cascade is activated, which leads to the formation of other proteins. The gene of one of these proteins, luciferase, was previously artificially introduced. Stimulation of the protein expression additionally leads to the formation of luciferase, which in the presence of ATP induces the emission of photons (so-called luminescence), which then can be measured photometrically. The intensity of the luminescence is proportional to the stimulation of the receptors. Dopamine agonists stimulate the luminescence while antagonists do not lead to a specific effect. However, antagonists inhibit the luminescence induced via either dopamine or agonist. The activity in different substance concentrations is represented in % of maximal activity via the endogenous ligand or a suitable agonist. The EC50 value (concentration at 50 % activation) and the slope are determined using regression analysis. Using the Cheng-Prusoff-equation, the Ki value is determined, which then is used for comparison: the lower the Ki value, the higher the affinity and activity. In regard to the effect of (S)-2-N-propylamino-5-hydroxytetralin on dopamine receptors, the values provided in Table 2 were found.

3. Example: In vitro reaction of a prodrug into the active substance

From liver cell homogenates from human, primate, dog, rat or mouse, the microsome fraction which comprises the primary metabolic enzymes recovered by differential centrifugation; alternatively, the cytoplasmic fraction can also be recovered. The subcellular fraction is suspended with a buffer to obtain a solution with a defined amount of protein. After addition of 1 µM of the prodrug to be tested, an incubation follows at 37°C for 60 min. Subsequently, (S)-2-N-propylamino-5-hydroxytetralin is quantified using HPLC/UV or using HPLC/MS and put into relation with the used amounts. For detailed analysis, concentration curves or time courses are investigated.

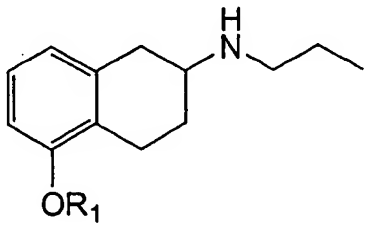
4. Example: Depot suspension

(a) 1411.2 g Miglyol 812 is weighed out into a Duran flask. 14.4 g Imwitor 312 was added to the Miglyol and subsequently was heated for 30 minutes to 80°C while stirring. The clear solution was cooled to room temperature and filtered.

(b) 1188 g of the solution produced in (a) was transferred to a glass laboratory reactor, 12 g of active agent was added and homogenized for 10 minutes with an ultraturrax at 10,000 rpm under nitrogen. The suspension was filled with running ultraturrax (2,000 rpm) in brown glass flasks.

Amended Claims

1. Pharmaceutical composition, comprising (S)-2-N-propylamino-5-hydroxytetralin or the salts or prodrugs thereof, wherein the prodrug is of the general formula I:



wherein R1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acetal, ketal, -C(O)NR2R3, -C(O)NHR2, -P(O_2H)OR2, -P(O_2H)R2,

wherein R2 and R3 are respectively selected from H, C1-6-alkyl, C3-10-cycloalkyl, benzyl or phenyl.

2. Pharmaceutical composition according to claim 1, wherein R1 is selected from C1-6-alkylcarbonyl, C3-10-cycloalkylcarbonyl, benzoyl, -C(O)NR2R3 and -C(O)NHR2.

3. Pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition is designed for transdermal, transmucosal or parenteral administration.

4. Use of (S)-2-N-propylamino-5-hydroxytetralin or the salts or prodrugs thereof according to claim 1 or 2, for the preparation of a medicament for treatment or prophylaxis of a disease selected from the group of depressions, anxiety disorders, sexual dysfunctions, galactorrhoe, acromegaly, glaucoma, cognitive disorders, restless leg syndrome, attention deficit hyperactivity syndrome (ADHS), hyperprolactinemia, hyperprolactinoma, eating disorders, DOPA-sensitive dyskinesias, Parkinson associated movement disorders, DOPA and neuroleptics induced movement disorders, cocaine-, alcohol-, opiate- and nicotine addictions, neurodegenerative disorders or for ablactation.

5. Use according to claim 4, wherein the disease is selected from the group consisting of restless leg syndrome, L-DOPA-sensitive dyskinesias, Parkinson associated movement disorders, L-DOPA- and neuroleptics-induced movement disorders, as well as cocaine-, alcohol-, opiate- and nicotine addictions.

6. Use according to any one of the preceding claims, wherein the disease is a movement disorder which is
   (a) Morbus Parkinson associated,
   (b) induced by L-DOPA, or
   (c) induced by neuroleptics.